

**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
APPLICATION FOR LETTERS PATENT

APPLICANTS	:	Kenneth Weisman and Michael E. Goldberg
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INVENTION	:	METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS
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TO ALL WHOM IT MAY CONCERN:

Be it known that we, Kenneth M. Weisman and Michael E. Goldberg, citizens of the United States of America, residing above, have made a certain new and useful invention as set forth above of which the following is a specification.

This application claims the benefit of the filing dates of Provisional Patent Applications Serial No. 60/049,003 (filing date June 9, 1997); 60/049,160 (filing date June 9, 1997); 60/049,746 (filing date June 12, 1998); 60/049,162 (filing date June 9, 1997); 60/049,169 (filing date June 9, 1997); 60/041,070 (filing date March 18, 1997).

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## BACKGROUND OF THE INVENTION

There are many steps in the biosynthesis and utilization by the tissues of testosterone. Testosterone is made mostly in the testicles. A lesser amount is made in the adrenals. Production is stimulated by secretion of Gn RH or LHRH by the brain, which causes secretion of luteinizing hormone (LH) by the pituitary, which causes the testicles to make testosterone. Testosterone then flows into the blood stream and is absorbed by the target cells. Here it binds to a receptor and is transported into the cell and converted to dihydrotestosterone. This is bound and carried to the nucleus of the cell where it redirects cellular activity by turning on and off DNA. Hormonal manipulation is a term which refers to the reduction of testosterone or its effects by blocking any step in the above process in order to gain a desired effect. Until now the uses of hormonal manipulation include for example treating prostatic carcinoma, and treatment for baldness.

The present invention involves the use of hormonal manipulations in the prevention and treatment of atherosclerosis, coronary heart disease, stroke and peripheral vascular disease.

Leuprolide acetate is a synthetic nonapeptide of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH), the chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate salt sold under the trade name Lupron or Lupron Depot, as identified by US patent no. 4,897,256, the entire disclosure is incorporated by

reference herein, is known for use in the treatment of prostatic carcinoma. Leuprolide is a potent inhibitor of gonadotropin secretion known to decrease levels of LHRH, LH and Testosterone.

Goserelin Acetate, a synthetic decapeptide analogue of LHRH or GnRH, is chemically described as an acetate salt of [D-Ser(Bu<sup>t</sup>)<sup>6</sup> Azygly<sup>10</sup>] LHRH. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu)-Leu-Arg-Pro-Azgly-NH<sub>2</sub> acetate [C59H84N18O2] sold under the trade name Zoladex, as identified by the US patent no. 5,510,460, the entire disclosure is incorporated by reference herein, is known for the use in treatment of prostatic carcinoma. Goserelin acetate is a potent inhibitor of gonadotropin secretion known to reduce levels of GnRH or LHRH, LH and Testosterone.

Nilutamide, a nonsteroidal, orally active, antiandrogen, having the chemical name 5,5-dimethyl 3-[4-nitro-3-(trifluoromethyl)phenyl] 2,3-imidazolidinedione, sold under the trade name Nilandron, as identified by US patent no. 5,023,088, the entire disclosure is incorporated by reference herein, is known for use in treatment of prostatic carcinoma.

Flutamide, an acetanilid, nonsteroidal androgen having the chemical name, 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl] propanamide sold under the trade name Eulexin, as identified by US patent nos. 3,995,060 and 4,474,813, the entire disclosure of which are incorporated by reference herein, Flutamide is known for use in treatment of prostatic carcinoma.

Bicalutamide, a non-steroidal antiandrogen, chemical name is propanamide, N-(4 cyano-3-(trifluoromethyl)phenyl)-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-(+/-) sold under the trade name Casodex, as identified by US patent no. 4,636,505, the entire disclosure is incorporated by reference herein, is known for use in treatment of prostatic carcinoma.

A retrospective study was performed which compared the rates of patient reported heart attack in several groups: 1 - control group of males entering the urology office for any routine complaint. 2 - a group of prostate cancer patients treated with Leuprolide acetate, a LHRH inhibitor. 3 - a group of prostate cancer patients treated with Goserelin acetate (Zoladex), a LHRH inhibitor. 4 - a group of prostate cancer patients not treated with hormonal manipulation (neither Leuprolide or Goserelin). 5 - a group of patients treated with Finasteride (another form of hormonal manipulation). 6 - all patients on LHRH inhibitors (group 2 + group 3).

*INS > B<sup>3</sup>* The patients on either ~~Leuprolide or Goserelin~~ were treated with the recommended doses indicated for the treatment of prostatic carcinoma, at either one or three month intervals depending on the preparation used. Leuprolide was dosed at 7.5 mg monthly (single intramuscular injection) or at 22.5 mg at 3 month intervals (single intramuscular injection). Goserelin was dosed at 3.6 mg monthly (subcutaneous injection) or at a dose of 10.8 mg at 3 month intervals (subcutaneous injection).

The various groups of office patients were given a questionnaire. In groups 2, 3 and 5 only those on drug for at least one year were considered. Cardiac event is defined as either the history of a heart attack or occurrence of coronary artery bypass or angioplasty. In control groups only events occurring in the 3 years prior to the questionnaire are charted. The results were as follows:

	No Patients	Cardiac Events	Subject Years	Events/Year
Group 1 (control no cancer)	247	26	741	.0351
Group 4 (control cancer patients)	69	6	207	.0290
Total Control (Groups 1 + 4)	316	32	948	.0338
Group 2 ( <del>Lupron</del> )	28	1	118	.00847
Group 3 ( <del>Zoladex</del> )	25	1	62	.0161
Group 5 - (Finasteride)	91	4	242	.0165
Group 6 (antiLHRH) groups 2 + 3	50	2	180	.0111

The observed difference between the proportions of Total Control vs Group 6 (LHRH) is .0226. 95% Confidence Interval for the difference between the proportions is .00350 to .0418. Patients treated with LHRH inhibitors had fewer heart attacks than controls.

The observed difference between the proportions of Group 2 (Lupron) and Total Control is .0253. 95% Confidence Interval for the difference between the proportions is .00514 and .0454. Patients treated with Leuprolide acetate had fewer heart attacks than controls.

The observed difference between the proportions of Group 3 and Total Control is .0177. Patients treated with Goserelin (Zoladex) had fewer heart attacks than controls.

The observed difference between the proportions of Group 1 (Control) and Group 5 (Finasteride) is .0186. 90% Confidence Interval for the difference between the proportions is .00103 to .0361. Patients treated with Finasteride had fewer heart attacks than control.

Without further elaboration the foregoing will so fully illustrate our invention that others may, by applying current and future knowledge, adopt the same for use under various conditions of service.